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Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function (Review)

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[Intervention Review]

Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

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ABSTRACT

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) can play a major role in the management of acute pain in the peri-operative period. However, there are conflicting views on whether NSAIDs are associated with adverse renal effects.

Objectives

The primary objective of this review was to determine the effects of NSAIDs on postoperative renal function in adults with normal preoperative renal function.

Search methods

Electronic searches for relevant randomised and quasi-randomised controlled trials in Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were performed. Attempts were also made to identify trials from citation lists of relevant trials, review articles and clinical practice guidelines. Handsearching of conference abstracts published in major anaesthetic journals was also performed. (Search date: 7 February 2003)

Selection criteria

The inclusion criteria were randomised or quasi-randomised comparisons of individual NSAIDs with either each other or placebo for treatment of postoperative pain, with relevant postoperative renal outcome measures, in adult surgical patients with normal renal function.

Data collection and analysis

The data was extracted independently by two reviewers. The primary outcome measure was creatinine clearance within the first two days after surgery. Secondary outcome measures included serum creatinine, urine volume, urinary sodium level, urinary potassium level, fractional excretion of sodium, fractional excretion of potassium, need for dialysis and need for diuretic or dopamine treatment for renal insufficiency. Weighted mean differences for continuous outcomes and relative risk for dichotomous outcomes were estimated.

Main results

Nineteen trials (n = 1204) fulfilled the selection criteria for this review. NSAIDs reduced creatinine clearance by 16ml/min (95%CI 5 to 28) and potassium output by 38mmol/day (95%CI 19 to 56) on the first day after surgery compared to placebo. There was no significant difference in serum creatinine on the first day (0 umol/L, 95%CI -5 to 4) compared to placebo. No significant reduction in urine volume during the early postoperative period was found. There was no significant difference in serum creatinine in the early postoperative period between patients receiving diclofenace and ketorolac (or indomethacin). No cases of postoperative renal failure requiring dialysis were described. The trials were homogenous for the primary outcome.

Authors' conclusions

NSAIDs caused a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function. NSAIDs should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment.

PLAIN LANGUAGE SUMMARY

NSAIDs used for pain relief after surgery may have only small, temporary negative effects on kidney function in adults with normal renal function

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to try and relieve pain after surgery. However, there have been concerns about the possible harmful effects of these drugs on the kidneys. The review of trials found that NSAIDs can cause small, temporary negative effects on the kidneys in adults, but no one in the trials experienced renal failure or serious kidney problems. These results may not apply to children or adults with decreased kidney function

BACKGROUND

Optimal postoperative pain management can include the selective use of nonsteroidal anti-inflammatory drugs (NSAIDs) with or without supplemental opioids. The Royal College of Anaesthetists recently published Guidelines for the use of nonsteroidal anti-inflammatory drugs in the peri-operative period, an overview of the benefits and risks of using NSAIDs (RCA 1998). It concluded that in patients who had undergone major surgery, NSAIDs were not sufficiently effective as the sole agent and that renal function should be monitored regularly in these patients and in at-risk patients (RCA 1998).

The peri-operative use of NSAIDs may be limited because of concern with side effects relating to the gastrointestinal, coagulation and renal systems (Strom 1996; Feldman 1997; Romsing 1997). Recent attention has been given to the possibility of renal toxicity caused by the use of NSAIDs during the peri-operative period (Myles 1998). NSAIDs may produce either acute, reversible or permanent renal toxicity and a variety of effects on electrolyte and water homeostasis (Murray 1993). The most important renal complication after surgery is acute renal failure. Acute renal failure is characterised by a deterioration of renal function over a period of hours to days, resulting in the failure of the kidney to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis (Thadhani 1996). Morbidity and mortality are highly associated with postoperative acute renal failure (Novis 1994). While the definition of acute renal failure and renal insufficiency varies among studies, one study showed that the overall incidence of postoperative renal insufficiency was 18% after major surgery, with a subsequent hospital mortality rate of 13% (Hou 1983).

Although there have been case reports describing adverse renal effects of NSAIDs (Smith 1993; Sivarajan 1997), the evidence from randomised controlled trials (RCTs) is inconclusive. Several such studies (Aitken 1992; Perttunen 1992; Power 1992; Irwin 1995) showed that NSAIDs caused changes in electrolyte balance and urine output. In contrast, others have failed to show any significant effect of NSAIDS on renal function (Turner 1994; Varrassi 1994; Brinkmann 1998; Perttunen 1999, Jones 2000, Laisalmi 2001a). Most of these RCTs were limited to the effects of NSAIDs on the renal system within the first 48 hours in adults with normal renal function, and did not address the longer term effects on renal function or the safety of NSAIDs in patients with im-

paired renal function. In some of these trials, the results may have been imprecise because the sample size was insufficient to detect important differences. Therefore, it is unclear whether there is a clinically significant effect of NSAIDs on renal function in the early postoperative period.

OBJECTIVES

To assess the effects of NSAIDs on postoperative renal function in adults with normal preoperative renal function.

We wished to test the following hypotheses:

1. Treatment with NSAIDs is more harmful on the renal system than placebo in the early postoperative period (first 48 hours after surgery)

2. Individual NSAIDs have similar harmful effects on the renal system in the early postoperative period (first 48 hours after surgery)

METHODS

Criteria for considering studies for this review

Types of studies

1. All RCTs and quasi-randomised (allocation based on alternation, date of birth, hospital medical record number) controlled trials of NSAID treatment versus placebo for treatment of postoperative pain.
2. All RCTs and quasi-randomised controlled trials that compared two or more NSAID for treatment of postoperative pain.

Types of participants

All adult surgical patients with normal preoperative renal function.

Types of interventions

NSAID treatments (ketorolac, ibuprofen, diclofenac, indomethacin, tenoxicam, ketoprofen) versus placebo. Variable doses and all routes of administration of NSAID treatment during the peri-operative period were considered.

Types of outcome measures

Each of the following outcomes (within the first 48 hours after surgery) were recorded where available

Primary outcome

- creatinine clearance

Secondary outcomes

- serum creatinine
- urine volume
- urinary sodium level
- urinary potassium level
- fractional excretion of sodium
- fractional excretion of potassium
- need for dialysis
- need for diuretic treatment for renal insufficiency
- need for dopamine treatment for renal insufficiency

Long term harmful effects of NSAIDs are not considered, and the need for dialysis is the most important for the consumer.

Search methods for identification of studies

Relevant trials were obtained from the following sources:
- The Cochrane Controlled Trials Register (Issue 1, 2003)
- Electronic databases: MEDLINE 1966-February 2003, EMBASE 1988-February 2003
- Reference lists of relevant articles, reviews, trials and clinical practice guidelines (NHMRC 1999; RCA 1998)
- Pharmaceutical industry representatives
- Handsearching conference abstracts (1990 to May 1999) published in Acta Anaesthesiologica Scandinavica, Anaesthesia, Anaesthesia and Intensive Care, Anesthesia and Analgesia, Anesthesiology, British Journal of Anaesthesia and Canadian Journal of Anaesthesia.

There were no language restrictions. The first author was contacted to clarify issues related to data extraction.

All publications which described RCTs, clinical trials, and controlled trials were obtained using the optimal sensitive search strategy method (Chalmers 1995). In addition, the following MESH and textwords were included in the MEDLINE electronic search strategy: NSAIDs, nonsteroidal, kidney failure, postoperative renal failure, postoperative. The MEDLINE search was modified to search for relevant trials in EMBASE.

Data collection and analysis

The selection of trials for inclusion in the review was performed independently by the reviewers (AL and MC). Trials were examined for duplicate data. Data was abstracted independently, by AL and MC, using a standardised data collection form. Discrepancies were resolved by discussion, or, if no consensus was reached, advice was sought from a third party (JC). The quality of eligible trials were assessed independently, under open conditions. The quality of allocation concealment was graded as A-adequate, B-unclear, or C-inadequate, as previously described (Schulz 1995). Blinding, losses to follow-up, method of randomisation, intention-to-treat analysis and power calculations were recorded.

The duration of treatment, type, and dose of NSAIDs, patient population, type of surgery, and anaesthetic details were collected. The primary outcome was change in creatinine clearance on Day 1 (0 to 24th hours) and Day 2 (24th to 48th hour) after surgery. A creatinine clearance reduction of 50% was chosen a priori as the threshold for a clinically important change. If the article reported measurements taken at multiple time points, the values at or near 24 or 48 hours after surgery were selected for analyses, because the 24 and 48 hour time points were most often reported in these studies. In cases where results were presented in graphs and no actual data were given, the data were extracted from the graphs or the primary author was contacted for clarification.

The DerSimonian and Laird random-effects model was used to combine data for both continuous and dichotomous outcomes, because we expected that the treatments and conditions in these studies would be heterogeneous. This model incorporates both between-study (different treatment effects) and within-study (sampling error) variability (Mosteller 1996). The pooled relative risk (RR) and 95% confidence interval (95%CI) were calculated for dichotomous data (need for dialysis, diuretic treatment for renal insufficiency and dopamine treatment for renal insufficiency). For continuous outcomes, the mean and standard deviation for each treatment group, before and after the operation, were collected. The mean change from baseline to follow-up, between treatment groups, was not given in trials. Therefore, as the correlation coefficient between preoperative and postoperative measures was unknown, we assumed a correlation of 0.50 (Follmann 1992). A sensitivity analysis was carried out assuming zero correlation. The standard deviation between preoperative and postoperative measures for each treatment group was estimated using a method outlined in the Cochrane Collaboration Handbook. When the median and interquartile range were reported, we assumed that the mean was equivalent to the median and estimated the standard deviation to be interquartile range/1.35 (O'Rourke 2002).

For each continuous outcome, the mean difference in each study was defined:

mean difference = [NSAIDs (post - pre)] - [Placebo (post - pre)]

where "post" represented a postoperative measure and "pre" represented a preoperative measure. A postoperative measure was either at Day 1or Day 2 after surgery.

A weighted mean difference (WMD) method was used to pool continuous data for each of the following outcomes: creatinine clearance, serum creatinine, urine volume, sodium output, potassium output, fractional excretion of sodium and fractional excretion of potassium. These were analysed separately for Day 1 and Day 2. These results are reported as WMD and 95%CI.

Heterogeneity was analysed using the Q-statistic with a threshold for the p value of less than 0.10. Where heterogeneity (inter-study variation) was found, we tried to discover the reason for it. Subgroup analyses were done to estimate the robustness of results according to the type and dose (single versus multiple dose regimen, or comparison of two or more dosage regimen) of NSAID given.

RESULTS

Description of studies

Twenty-three RCTs of NSAIDs for postoperative pain with relevant renal outcome measures were identified.

Trials excluded from this review

Four trials were excluded from the review. One of these (Fredman 1999) examined the effect of diclofenac on intra operative renal blood flow and glomerular filtration rate, and did not collect postoperative renal outcome measures. The other study (Horneffer 1990) was excluded because NSAIDs (ibuprofen or indomethacin) were administered two days after cardiac surgery to treat postpericardiotomy syndrome. Acute renal failure up to 30 days after surgery was the outcome used in one multi-centered RCT (Forrest 2002). No additional relevant renal outcome measures were reported in the second paper by Laisalmi (Laisalmi 2001b).

Trials included in this review

Nineteen RCTs met the criteria for inclusion in the review. The trials were conducted between 1992 and 2001. The participants were all adults with normal preoperative renal function. Patients underwent various types of surgery, ranging from minor orthopaedic surgery (Irwin 1995) to major abdominal surgery (Castiglione 1997; Rao 2000). Where specific details were given, surgery was on an elective basis. All patients underwent general anaesthesia, with additional regional anaesthesia in three studies (Perttunen 1992; Brinkmann 1998; Jones 2000). Adequate preoperative and postoperative hydration treatment was described in only one study (Slaven 1998). We did not collect data on fluid or blood losses during surgery. There was insufficient data for meta-analysis in nine studies (Nuutinen 1991; Parker 1994; Ready 1994; Turner 1994; Varrassi 1994; Kostamovaara 1996; Castiglione 1997; Rao 2000; Chow 2001).

NSAIDs examined included diclofenac, ketorolac, indomethacin, ketoprofen, tenoxicam and ibuprofen. The route of NSAID administration varied (intravenous bolus, intravenous infusions, suppositories, intramuscular, or combinations of these). A single dose NSAID regimen was used in three studies (Brinkmann 1998; Slaven 1998; Jones 2000). Creatinine clearance was collected in seven studies (Nuutinen 1991; Aitken 1992; Power 1992; Irwin 1995; Brinkmann 1998; Slaven 1998; Jones 2000) but sufficient data for meta-analysis was available in six studies (Aitken 1992; Power 1992; Irwin 1995; Brinkmann 1998; Slaven 1998; Jones 2000). The intermittent ketorolac arm (10mg every four hours intramuscular) was chosen randomly over the continuous ketorolac arm (intramuscular infusion) in the Aitken 1992 trial for the purposes of this review. Data from the Perttunen 1999 trial using the diclofenac arm, not ketorolac arm, was pooled for comparisons between NSAIDs and placebo. Diclofenac, not ketoprofen or indomethacin, was pooled for comparisons between NSAIDs and placebo in another trial (Hynninen 2000).

Risk of bias in included studies

Seven trials (Ready 1994; Turner 1994; Perttunen 1999; Hynninen 2000; Jones 2000; Rao 2000; Laisalmi 2001a) had adequate allocation of concealment (A). The remaining trials received an allocation score of B (unclear). Double-blinding was used in 16 trials and single blinding was used in one trial (Slaven 1998). The majority of trials did not specifically state that they had used an intention-to-treat analysis. Power calculations were done in three trials (Hynninen 2000; Jones 2000; Rao 2000). Withdrawals were less than 10% in all trials, except Chow 2001(15%) and Ready 1994 (31%).

Effects of interventions

NSAIDs versus placebo

All studies pooled for analysis were homogeneous except for serum creatinine on Day 2. There were no reported cases of postoperative renal failure requiring dialysis. The pooled risk of renal insufficiency requiring postoperative frusemide treatment for two trials (Power 1992; Brinkmann 1998) was no greater in the NSAIDs group than the placebo group (RR 1.52, 95%CI 0.68 to 3.36). Dopamine was routinely given to all patients undergoing infrarenal abdominal aortic surgery (Brinkmann 1998). In another trial (Power 1992), one patient in the diclofenac group was given dopamine and frusemide for postoperative renal insufficiency but subsequent analysis showed that this patient had pre-existing renal impairment.

When creatinine clearance was pooled from all trials, NSAIDs significantly reduced creatinine clearance by 16 ml/min (95%CI 5 to 28) on Day 1. This was equivalent to 18% (95%CI 6 to 31%) reduction from the preoperative level. A sensitivity analysis (assuming zero correlation between measurements over time) showed that NSAIDs reduced creatinine clearance by 1 to 36% on Day 1. On Day 2, there was no significant reduction. A subgroup analysis based on dosing regimen showed that multiple NSAID dosing was associated with a significant reduction in creatinine clearance on Day 1 (-25ml/min, 95%CI -7 to -42). In comparison, single NSAID dose administration in two studies (Brinkmann 1998; Slaven 1998) was not significantly associated with a reduction in creatinine clearance (-10ml/min, 95%CI -26 to +5). However, overall comparisons of the subgroups showed no significant difference (P = 0.23). The overall comparison of the subgroups (multiple versus single dosing) on Day 2 showed no significant difference (P = 0.19).

There was no significant difference in serum creatinine between NSAIDs and placebo on Day 1. There was heterogeneity in the trials with Day 2 serum creatinine, which could not be explained by the level of allocation concealment. There was significant heterogeneity (P = 0.02) in the trials with adequate allocation concealment (Perttunen 1999; Jones 2000; Laisalmi 2001a).

Despite an inadequate definition of oliguria, the proportion of patients given ketorolac or placebo who became oliguric was similar (4% versus 3% respectively; P = 0.72) (Ready 1994). There was no significant reduction in urine volume on Day 1 (-15 ml/min, 95%CI -32 to +1) or on Day 2 (-3 ml/min, 95%CI -19 to +14) after surgery.

There was no significant reduction in urinary sodium levels on Day 1 or Day 2. However, there was significant reduction in urinary potassium levels on Day 1 (-38mmol/L, 95%CI -56 to -19), but not on Day 2 (-15mmol/L, 95%CI -39 to +9). The reductions in fractional sodium and potassium excretion were not significant on Day 1 or on Day 2

NSAID versus NSAID

There were two trials (Perttunen 1999; Hynninen 2000) that directly compared different types of NSAIDs. There was a significant reduction in serum creatinine associated with diclofenac compared to ketoprofen on Day 1(Hynninen 2000).

There was one trial (Castiglione 1997) that assessed two ketorolac dose regimens (270 mg versus 240 mg over 48 hours). They found no significant differences in serum creatinine levels on Day 2 between the two regimens.

DISCUSSION

This systematic review has shown that NSAIDs caused a clinically unimportant reduction in renal function on the first day after surgery in patients with normal preoperative renal function. The reduction in creatinine clearance on the first day by NSAIDs was up to 31% (up to 36% using sensitivity analysis of zero correlation of measurements over time), which is less than the clinically important reduction threshold set *a priori.* The fact that this reduction did not affect urine volume or that no patients required dialysis confirms that it is clinically unimportant. We noted that one patient with pre-existing renal disease received both frusemide and dopamine for the treatment of renal insufficiency, probably caused by the use of diclofenac (Power 1992). Another patient given ketoprofen had transient oliguric renal failure, of which hypovolaemia was a contributing cause (Rao 2000). There was no evidence of a reduction in creatinine clearance by NSAIDs on the second day after surgery.

Overall, transient postoperative creatinine clearance and electrolyte homeostasis disturbances attributed to the use of NSAIDs were found. The mechanism by which NSAIDs affect the renal system is complex. Inhibition of prostaglandin synthesis by NSAIDs can decrease distal tubular flow rate and sodium delivery, by reducing the glomerular filtration rate and increasing tubular reabsorption of sodium (Bugge 1995). Inhibition of prostaglandins leads to a moderate decline in aldosterone, which may contribute to potassium retention (Bugge 1995). The mode of action at the cellular level of NSAIDs in producing renal impairment is reviewed elsewhere (Murray 1993).

There was no strong evidence that NSAIDs caused postoperative renal failure in adults with normal preoperative renal function. None of the adults required dialysis for acute renal failure. A retrospective cohort (Feldman 1997) of inpatients receiving parenteral ketorolac and opioids for two days showed that the ketorolac group were at no greater risk of acute renal failure compared to the opioid group (adjusted RR 0.86, 95%CI 0.63 to 1.17). However, it is plausible that NSAIDs may cause postoperative renal failure in patients with pre-existing impaired renal blood flow, such as the elderly, those with heart failure or shock, or patients exposed to other nephrotoxic agents (Thadhani 1996). The information about risk factors for postoperative renal impairment has mainly been derived from a qualitative systematic review (Novis 1994) of observational studies and case reports (Smith 1993; Sivarajan 1997).

A limitation of this review was the use of several surrogate measures of renal function for postoperative renal failure. These renal function tests have varying sensitivity and specificity for predicting the onset of peri-operative renal dysfunction (Kellen 1994). While serial determination of creatinine clearance is one of the most sensitive tests for predicting the onset of peri-operative renal dysfunction (Kellen 1994), creatinine clearance involving urine collections over 24 hours overestimates the glomerular filtration rate by 13% (Waller 1991). This confirms our view that the reduction in creatinine clearance was clinically unimportant. As testing creatinine clearance is time-consuming and labour intensive (Kellen 1994), few studies included in this systematic review collected creatinine clearance for more than a day. The Aitken 1992, Power 1992 and Jones 2000 trials suggest that there was a trend towards normal renal function on the second day after surgery after the use of NSAIDs.

Another consideration is that the different NSAIDs were combined to assess the overall adverse renal effects caused by this class of drugs and there was little evidence of statistical heterogeneity between the studies. All trials used the recommended maximum doses of NSAIDs in adults with normal baseline renal function. While the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition ratios would be different for various NSAIDs (Cryer 1998), there is no direct and current evidence to suggest that this makes a difference to the risk of renal impairment. Direct comparisons between diclofenac and ketorolac (Perttunen 1999) and diclofenac and indomethacin (Hynninen 2000) showed similar minor effects on serum creatinine. There was some evidence that ketoprofen may be associated with a 20% increase in serum creatinine compared with diclofenac (Hynninen 2000).

AUTHORS' CONCLUSIONS

Implications for practice

While the use of NSAIDs as sole analgesics has not been justified, the efficacy of NSAIDs as components of multimodal analgesia has been confirmed (NHMRC 1999). In considering the adverse renal effects of NSAIDs, this review has shown that there was a clinically unimportant transient reduction in renal function in the early postoperative period in a wide variety of surgical settings in patients with normal preoperative renal function. It should be noted that the findings may not be transferable to paediatric patients (in whom the renal effects of postoperative NSAIDs have not been adequately studied) or to those patients with pre-existing abnormal renal function. NSAIDs should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment.

Implications for research

Recent work suggests that different types of NSAIDs inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) to a varying extent (Cryer 1998). COX-1 is responsible for the production of prostaglandins in all tissues, while COX-2 is expressed only after trauma or inflammation (Vane 1997). NSAIDs that have a high COX-2: COX-1 ratio may have more potent anti-inflammatory activity with fewer side-effects than drugs with lower COX-2:COX-1 ratio (Vane 1997). COX-2 selective inhibitors have not been available in many countries or been used widely by anaesthetists for postoperative pain management. More trials comparing COX-2 selective inhibitors with older types of NSAIDs are needed to assess the incremental benefit of using COX-2 selective inhibitors and risk reduction of adverse renal effects. Further work is required to assess whether COX-2 selective inhibitors offer more benefits for patients with abnormal renal function.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aitken 1992

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. Four patients withdrew from study. No details about intention to treat analysis or power calculation
Participants	67 patients undergoing elective upper abdominal surgery. Exclusions: respiratory insufficiency, hepatic or renal impairment and abuse of alcohol or drugs
Interventions	Rx 1: ketorolac 12.5 mg/h IM infusion for 30 minutes during surgery then 2.5 mg/h for 47.5 hours, with normal saline injections every 4 hours Rx 2: ketorolac 10 mg every 4 hours IM for 48 hours, first dose during surgery. Pl: Intermittent and continuous infusions of saline to match other groups
Outcomes	Pre-operative and post-operative creatinine clearance, urine output, sodium output, potassium output
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Brinkmann 1998

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. No patients withdrew from study. No power calculation.
Participants	26 (22 males, 4 females) patients undergoing infrarenal aortic surgery. Exclusions: NSAIDs at least 7 days prior to surgery, history of renal disease, evidence for renal artery stenosis on preoperative aortography, drugs likely to alter renal function
Interventions	Rx: ibuprofen 400 mg IV before skin incision Pl: Placebo aliquot IV before skin incision
Outcomes	Pre-operative and post-operative creatinine clearance, fractional excretion of sodium, number of patients given diuretic or dopamine to treat post-operative renal insufficiency
Notes	All patients were given post-operative dopamine.

Brinkmann 1998 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Castiglione 1997

Methods	Blinding not stated. Randomised controlled trial. Randomisation method: not stated. No patients withdrew from study. No details about intention to treat analysis or power calculation
Participants	40 patients (18 to 70 years) undergoing major elective abdominal surgery. Exclusions: renal disease, hepatic disease, coagulopathy, history of allergy to NSAIDs or peptic ulcer
Interventions	Rx 1: 30 mg ketorolac IV at induction, 30 mg IV at skin closure then 30 mg IV every 6 hours for 48 hours. Rx 2: 30 mg ketorolac IV at skin closure then 30 mg IV every 6 hours for 48 hours
Outcomes	Pre-operative and post-operative serum creatinine.
Notes	Article in Italian.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Chow 2001

Methods	Double-blind randomised placebo controlled trial. 10 patients withdrew. Sample size not calculated. Per-protocol analysis.
Participants	55 (26 males, 29 females) patients undergoing laparoscopic urologic surgery. Exclusions: history of peptic ulcer/gastrointestinal bleeding, pregnancy, history of NSAID allergy/intolerance, or history of renal insufficiency (serum creatinine > 140 umol/L)
Interventions	Rx1: Ketorolac 15 to 30 mg IV every 6 hours up to 48 hours after surgery. First dose given at end of surgery. Pl: No details.

Chow 2001 (*Continued*)

Outcomes	Pre-operative and post-operative serum creatinine.	
Notes	Time at which post-operative serum creatinine was done within the first 48 hours was not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hynninen 2000

Methods	Double-blind randomised, placebo controlled trial. 6 patients withdrew. Sample size calculated. Per-protocol analysis done.	
Participants	114 adults undergoing coronary artery bypass grafting. Exclusion criteria: ejection fraction<20%, previous cardiac surgery, insulin dependent diabetes mellitus, weight > 100kg or <60 kg, renal insufficiency (creatinine > 130 umol/L) , allergy to propofol, morphine or NSAID, active peptic ulcer disease, history of gastrointestinal bleeding, age>75 years, warfarin, dipyridamole or heparin therapy preoperatively	
Interventions	Rx:1: Diclofenac 75 mg suppository twice a day after surgery. Rx2: Ketoprofen 100 mg suppository twice a day after surgery Rx: Indomethacin 100 mg suppository twice a day after surgery Pl: Placebo suppository twice a day after surgery	
Outcomes	Pre-operative and post-operative serum creatinine.	
Notes	1 patient was withdrawn after one dose of indomethacin because of serum creatinine increase > 20% postoperatively	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Irwin 1995

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method not stated. One patient withdrew from study. No details about intention to treat analysis or power calculation
Participants	22 males undergoing minor orthopaedic surgery. Exclusions: patients with respiratory, cardiac, hepatic or renal insufficiency, a history of peptic ulcer disease or allergy to aspirin, diclofenac or other prostaglandin inhibiting compounds
Interventions	Rx: Diclofenac 100 mg suppository before surgery then 100 mg on Day 1 Pl: Placebo suppository before surgery and on Day 1
Outcomes	Pre-operative and post-operative creatinine clearance, urine output, sodium output, potassium output, fractional excretion of sodium, fractional excretion of potassium
Notes	Day 2 measures were not used as no diclofenac was administered on Day 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Jones 2000

Methods	Double-blind, randomised placebo controlled trial. No patient withdrawal. Sample size calculated. Intention-to-treat analysis done.
Participants	30 women (50 to 70 years) undergoing major gynaecological surgery. Exclusions: renal or hepatic impairment, bleeding diathesis, hypersensitivity to NSAIDs, asthma, medications known to interfere with tenoxicam disposition
Interventions	Rx: Tenoxicam 20 mg IV given 2 hours before surgery. Pl: Normal saline IV given 2 hours before surgery.
Outcomes	Pre-operative and post-operative creatinine clearance, serum creatinine, fractional excretion of sodium and potassium
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Jones 2000 (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

Kostamovaara 1996

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. Three patients withdrew from study. No details about intention to treat analysis or power calculation
Participants	76 (26 males, 50 females) undergoing total hip (n = 62) or knee (n = 14) replacement. Exclusions: hepatic, renal or cardiac failure, bleeding or coagulation disorders, peptic ulcer, asthma, hypersensitivity to aspirin or other NSAIDs, or who were on cytostatic treatment
Interventions	Rx 1: 50 mg ketoprofen IV loading dose for 30 minutes, followed 50 mg ketoprofen infusion over following 11.5 hours. Rx 2: 100 mg ketoprofen IV loading dose for 30 minutes, followed 100 mg ketoprofen infusion over following 11.5 hours. Rx 3: 150 mg ketoprofen IV loading dose for 30 minutes, followed 150 mg ketoprofen infusion over following 11.5 hours. Pl: Isotonic saline infusion for 30 minutes, followed by saline over following 11.5 hours (n = 19)
Outcomes	Pre-operative and Day 2 serum creatinine.
Notes	Not pooled because serum creatinine was measured after drug had been eliminated (more than 5 half-life)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Laisalmi 2001a

Methods	Double-blind randomised placebo controlled trial. Randomisation: by sealed envelopes. No patient withdrew. Intention-to-treat analysis. No power calculation done.
Participants	30 women undergoing breast surgery. Exclusions: abnormal renal or hepatic function.
Interventions	Rx: Ketorolac 30 mg IM with premedication, at end of anaesthesia, and 6 hours after anaesthesia. Pl: Normal saline IM with premedication, at end of anaesthesia, and 6 hours after anaes-

Laisalmi 2001a (*Continued*)

	thesia	
Outcomes	Pre-operative and postoperative serum creatinine.	
Notes	No pre-operative urine output measure.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Nuutinen 1991

Methods	Randomisation method: not stated. Patients randomly allocated to diclofenac or placebo. No details about blinding. No loss to followup. No details about intention to treat analysis or power calculation	
Participants	Patients undergoing total hip replacement. Exclusions: no details.	
Interventions	Rx: Diclofenac infusion for 20 hours post-operatively, a bolus of 75 mg over 30 minutes, followed by infusion of 4mg/hour, then 50 mg three times a day for 10 days in ward. Pl: Normal saline infusion for 20 hours post-operatively, followed by dextropropoxyfen 65 mg orally	
Outcomes	Creatinine clearance, serum creatinine, urinary sodium level, urinary potassium level, urine volume	
Notes	Data insufficient for pooling. Abstract only.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Parker 1994

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. Twelve patients withdrew from study. No intention to treat analysis but power calculation done

Parker 1994 (*Continued*)

Participants	210 women undergoing abdominal hysterectomy. Exclusions: major organ dysfunction, history of allergic reactions to opioid analgesics or NSAIDs, bronchial asthma, gastrointestinal ulceration, bleeding disorders, or concurrent anticoagulant therapy	
Interventions	Rx: Ketorolac 60 mg IV bolus before end of surgery then 30 mg over 30 minutes every 6 hours for 72 hours Pl: 2ml normal saline IV before end of surgery then 20ml normal saline IV infusion over 30 minutes every 6 hours for 72 hours	
Outcomes	Pre-operative and hospital discharge serum creatinine.	
Notes	Median serum creatinine levels given but time of hospital discharge was variable among women	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Perttunen 1992

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. No patients withdrew from study. No power calculation.	
Participants	30 (24 males, 16 females) patients undergoing thoracotomy. Exclusions: aged more than 75 years; clincially manifest cardiac, renal or hepatic failure; history of gastrointestinal bleeding or peptic ulceration, haemorrhagic diathesis and asthma or allergy to aspirin or diclofenac; confusion, esimated preoperative FEV1<1L/s	
Interventions	Rx: diclofenac 25 mg IV bolus on arrival into recovery room then 2 mg/kg IV infusion for 48 hours Pl: saline infusion started with bolus dose of 25 ml in 15 minutes and continued with a constant rate of 2 ml/kg/d for 48 hours	
Outcomes	Pre-operative and post-operative serum creatinine, proportion of patients with urine output less then 100 ml during Day 1	
Notes	No pre-operative urine output measure.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Perttunen 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Perttunen 1999

Methods	Double-blind, randomised, placebo controlled trial. Randomisation: by sealed envelopes. No patients withdrew from study. No power calculation.
Participants	30 (14 males, 16 females) patients undergoing thoracoscopy. Exclusions: patients aged more than 75 years; with cardiac, renal or hepatic failure; history of gastrointestinal bleeding or peptic ulceration, haemorrhagic diathesis and asthma, or allergy to aspirin, NSAIDs or morphine; confusion, preoperative FEV1<60% of reference value, sleep apnoea
Interventions	Rx 1: diclofenac 17 mg IV bolus one hour before anaesthesia then 2 mg/kg/d IV infusion for 48 hours Rx 2: ketorolac 10 mg IV bolus one hour before anaesthesia then 1.2 mg/kg/d IV infusion for 48 hours Pl: saline bolus dose 17 ml in 30 minutes and continued with 2 ml/kg/d for 48 hours
Outcomes	Pre-operative and post-operative serum creatinine.
Notes	No pre-operative urine output measure.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Power 1992

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. One patient withdrew from study. No details about intention to treat analysis or power calculation
Participants	20 (17 males, 3 females) patients undergoing oesophagogastrectomy. Exclusions: history of peptic ulceration, asthma, previous reactions to NSAID, allergies, evidence of renal insufficiency, diuretic therapy and recent NSAID ingestion
Interventions	Rx: diclofenac 75 IM at induction then 4 doses (75 mg each) every 12 hours Pl: placebo with same diclofenac regimen.

Power 1992 (*Continued*)

Outcomes	Pre-operative and post-operative creatinine clearance, serum creatinine, urine output, sodium ouput, potassium output, number of patients on diuretic or dopamine to treat post-operative renal insufficiency
Notes	One patient in diclofenac group withdrawn due to low urine output and was later found to have had a reduced preoperative creatinine clearance (45ml/min)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rao 2000

Methods	Double-blind, randomised placebo controlled trial. One patient withdrew. Sample size calculated.
Participants	39 (22 males, 17 women) patients undergoing abdominal surgery. Exclusion: history of previous allergy to ketoprofen, aspirin and other NSAIDs, peptic ulcer disease, significant respiratory, renal or liver disease, history of depression, dementia or substance abuse, pregnant or lactating patients and patients with coagulopathies
Interventions	Rx: ketoprofen 100 mg IV at end of surgery and 12 hours after surgery Pl: Normal saline IV at end of surgery and 12 hours after surgery
Outcomes	Urine output
Notes	Oliguria not defined. One patient in ketoprofen group developed transient oliguric renal failure due to hypovolaemia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Ready 1994

Methods	Double-blind, randomised, placebo controlled trial. Randomisation: by computer, stratified by type of surgery. Sixty-five patients withdrew from study. Intention to treat analysis done but no power calculation.

Ready 1994 (*Continued*)

Participants	207 patients undergoing major orthopaedic, gynaecological or general surgery. Exclusions: know allergy, sensitivity or contraindications to any opioids, aspirin, or NSAIDs, history of active peptic ulcer within preceding 6 months, a history of bleeding problems or anticoagulant use within preceding 4 weeks, pregnancy or breast feeding, history of known or suspected alcohol or drug abuse, or a medical or psychiatric condition that would compromise ability to give informed consent
Interventions	Rx 1: 30 mg ketorolac IV bolus then 5 mg/h IV for 24 hours Rx 2: 30 mg IV bolus then 15 mg IV every 3 hours for 24 hours Pl: Placebo initial IV infusion bolus, IV infusion and IV bolus every 3 hours
Outcomes	Urine output
Notes	Oliguria was not defined. No significant difference in the incidence of oliguria between the three groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Slaven 1998

Methods	Single-blind, randomised, placebo controlled trial. Randomisation method: not stated. Number of patients withdrew from study unclear. No details about intention to treat analysis or power calculation
Participants	20 (16 males, 4 females) patients undergoing elective laminectomies. Exclusions: not stated
Interventions	Rx: tenoxicam 40 mg IV bolus before induction Pl: normal saline 5 ml IV bolus before induction
Outcomes	Pre-operative and post-operative creatinine clearance.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Turner 1994

Methods	Double-blind, randomised, placebo controlled trial. Randomisation: sequential selection of previously precoded envelopes. Two patients withdrew from study. No details about intention to treat analysis or power calculation
Participants	50 patients undergoing elective open cholecystectomy. Exclusions: History of peptic ulceration, bleeding disorder, renal impairment or haemorrhoids
Interventions	Rx: Indomethacin suppositories- 200 mg at end of surgery then 100 mg twice daily for 3 days. Pl: Placebo suppositories according to same treatment regimen
Outcomes	Pre-operative and post-operative serum creatinine
Notes	No pre-operative and post-operative serum creatinine measures given, rather the mean change was given for each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Varrassi 1994

Methods	Double-blind, randomised, placebo controlled trial. Randomisation method: not stated. Five patients withdrew from study. No details about intention to treat analysis or power calculation
Participants	100 patients undergoing elective cholecystectomy. Exclusions: pregnancy, history of peptic ulceration, coagulopathies, impaired renal function, allergy or intolerance to NSAIDs, alcohol or opioid abuse, children, aged more than 65 years
Interventions	Rx: ketorolac 30 mg IM before surgery then 2 mg/h IV infusion for 24 hours. Pl: normal saline 1ml IM then 2 ml/h IV infusion for 24 hours
Outcomes	Post-operative serum creatinine
Notes	No pre-operative serum creatinine data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Varrassi 1994 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rx = Treatment
Pl = Placebo

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Forrest 2002	Acute renal failure was defined as 100% increase in serum creatinine and/or oliguria, and/or dialysis, with evidence of increased blood urea and potassium, IV pyelogram, renal biopsy, x-rays and/or ultrasound at any time during the 30 days after surgery. No data given for the first 2 days after surgery
Fredman 1999	Did not collect postoperative renal outcome measures
Horneffer 1990	NSAIDs (ibuprofen or indomethacin) were administered two days after cardiac surgery to treat post-pericardiotomy syndrome
Laisalmi 2001b	No relevant postoperative renal outcome measures

DATA AND ANALYSES

Comparison 1. NSAIDs versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in creatinine clearance (ml/min)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Change in creatinine clearance on Day 1	6	141	Mean Difference (IV, Random, 95% CI)	-16.48 [-28.03, -4.94]
1.2 Change in creatinine clearance on Day 2	3	74	Mean Difference (IV, Random, 95% CI)	1.68 [-21.44, 24.79]
2 Change in serum creatinine (umol/L)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Change in serum creatinine on Day 1	6	185	Mean Difference (IV, Random, 95% CI)	-0.17 [-4.57, 4.23]
2.2 Change in serum creatinine on Day 2	4	100	Mean Difference (IV, Random, 95% CI)	2.10 [-7.48, 11.68]
3 Change in urine volume (ml/h)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Change in urine output on Day 1	3	72	Mean Difference (IV, Random, 95% CI)	-15.25 [-31.63, 1.13]
3.2 Change in urine output on Day 2	2	51	Mean Difference (IV, Random, 95% CI)	-2.90 [-19.40, 13.60]
4 Change in urinary sodium output (mmol/d)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Change in sodium output on Day 1	3	67	Mean Difference (IV, Random, 95% CI)	-37.07 [-79.43, 5.28]
4.2 Change in sodium output on Day 2	2	45	Mean Difference (IV, Random, 95% CI)	-11.34 [-48.82, 26.14]
5 Change in urinary potassium output (mmol/d)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Change in potassium output on Day 1	3	67	Mean Difference (IV, Random, 95% CI)	-37.50 [-55.91, -19.09]
5.2 Change in potassium output on Day 2	2	45	Mean Difference (IV, Random, 95% CI)	-14.79 [-38.62, 9.04]
6 Change in fractional excretion of electrolyte (%)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Change in sodium on Day 1	3	77	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.75, 0.34]
6.2 Change in sodium on Day 2	1	30	Mean Difference (IV, Random, 95% CI)	-0.6 [-1.35, 0.15]
6.3 Change in potassium on Day 1	2	51	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.02]
6.4 Change in potassium on Day 2	1	30	Mean Difference (IV, Random, 95% CI)	0.01 [-0.03, 0.05]
7 Renal insufficiency requiring postoperative frusemide treatment	2	46	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.68, 3.36]

Comparison 2. Multiple versus single NSAID dose regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in creatinine clearance (ml/min) on Day 1	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Multiple NSAID doses versus placebo	3	66	Mean Difference (IV, Random, 95% CI)	-24.63 [-42.29, -6.98]
1.2 Single NSAID dose versus placebo	3	75	Mean Difference (IV, Random, 95% CI)	-10.40 [-25.65, 4.86]
2 Change in creatinine clearance (ml/min) on Day 2	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Multiple NSAID doses versus placebo	2	44	Mean Difference (IV, Random, 95% CI)	-7.59 [-30.66, 15.47]
2.2 Single NSAID dose versus placebo	1	30	Mean Difference (IV, Random, 95% CI)	23.0 [-15.32, 61.32]

Comparison 3. NSAID versus NSAID

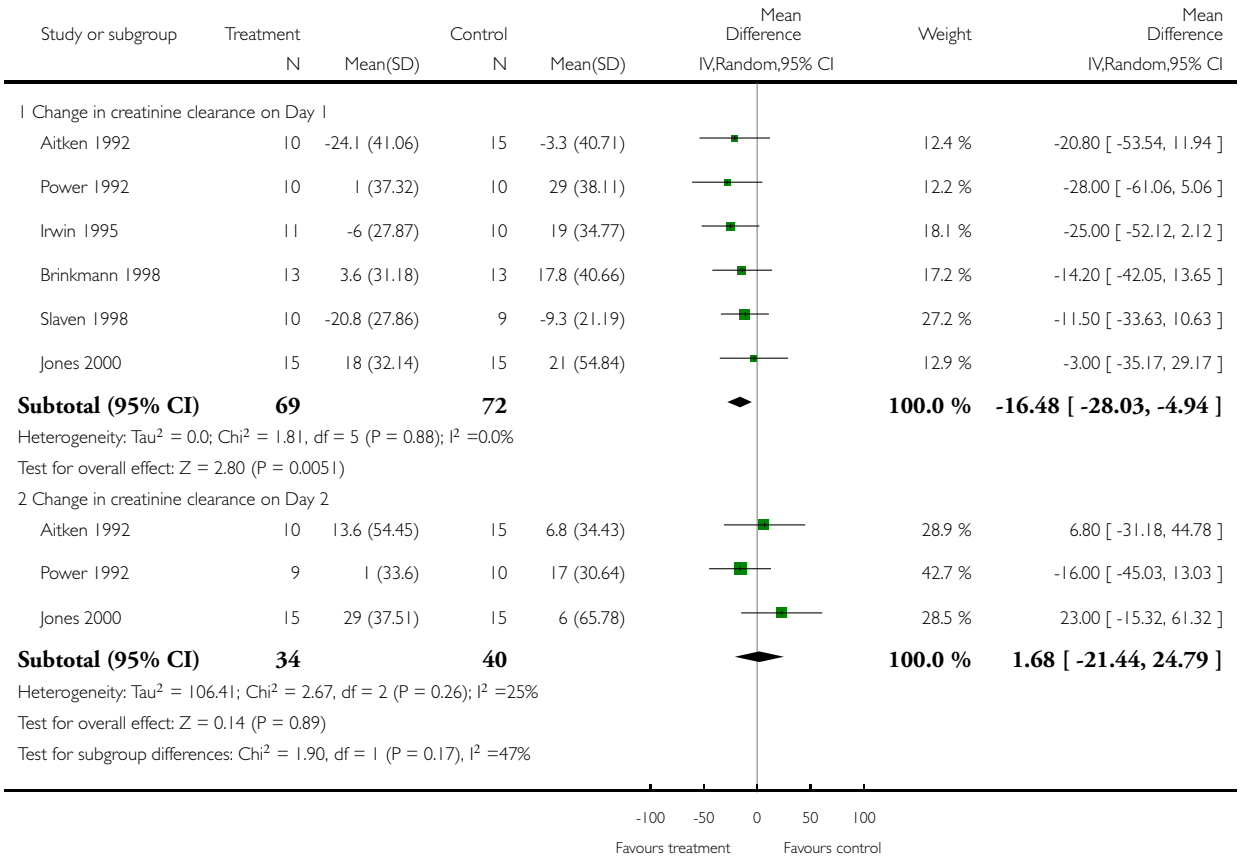
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diclofenac versus ketorolac	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Change in serum creatinine (umol/L) on Day 1	1	20	Mean Difference (IV, Random, 95% CI)	-4.0 [-14.98, 6.98]
1.2 Change in serum creatinine (umol/L) on Day 2	1	20	Mean Difference (IV, Random, 95% CI)	2.0 [-13.08, 17.08]
2 Diclofenac versus ketoprofen	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Change in serum creatinine (umol/L) on Day 1	1	56	Mean Difference (IV, Random, 95% CI)	-11.0 [-18.50, -3.50]
3 Diclofenac versus indomethacin	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Change in serum creatinine (umol/L) on Day 1	1	55	Mean Difference (IV, Random, 95% CI)	-2.85 [-7.23, 1.53]
4 Ketoprofen versus indomethacin	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Change in serum creatinine (umol/L) on Day 1	1	55	Mean Difference (IV, Random, 95% CI)	8.0 [-0.50, 16.50]

Analysis 1.1. Comparison 1 NSAIDs versus Placebo, Outcome 1 Change in creatinine clearance (ml/min).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 1 Change in creatinine clearance (ml/min)



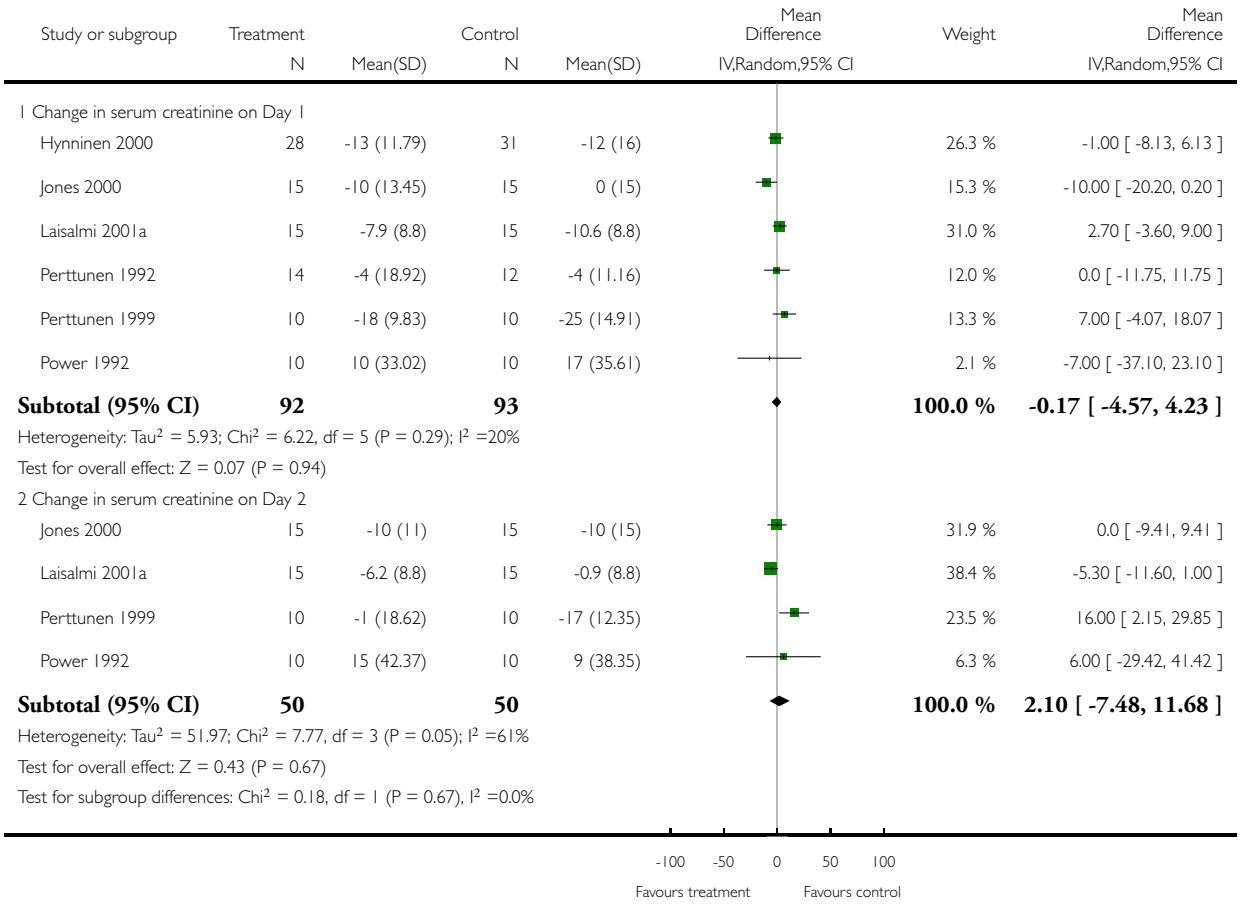
Analysis 1.2. Comparison 1 NSAIDs versus Placebo, Outcome 2 Change in serum creatinine (umol/L).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 2 Change in serum creatinine (umol/L)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Change in serum creatinine on Day 1							
Hynninen 2000	28	-13 (11.79)	31	-12 (16)		26.3 %	-1.00 [-8.13, 6.13]
Jones 2000	15	-10 (13.45)	15	0 (15)		15.3 %	-10.00 [-20.20, 0.20]
Laisalmi 2001a	15	-7.9 (8.8)	15	-10.6 (8.8)		31.0 %	2.70 [-3.60, 9.00]
Perttunen 1992	14	-4 (18.92)	12	-4 (11.16)		12.0 %	0.0 [-11.75, 11.75]
Perttunen 1999	10	-18 (9.83)	10	-25 (14.91)		13.3 %	7.00 [-4.07, 18.07]
Power 1992	10	10 (33.02)	10	17 (35.61)		2.1 %	-7.00 [-37.10, 23.10]
Subtotal (95% CI)	**92**		**93**			**100.0 %**	**-0.17 [-4.57, 4.23]**
Heterogeneity: Tau² = 5.93; Chi² = 6.22, df = 5 (P = 0.29); I² =20%							
Test for overall effect: Z = 0.07 (P = 0.94)							
2 Change in serum creatinine on Day 2							
Jones 2000	15	-10 (11)	15	-10 (15)		31.9 %	0.0 [-9.41, 9.41]
Laisalmi 2001a	15	-6.2 (8.8)	15	-0.9 (8.8)		38.4 %	-5.30 [-11.60, 1.00]
Perttunen 1999	10	-1 (18.62)	10	-17 (12.35)		23.5 %	16.00 [2.15, 29.85]
Power 1992	10	15 (42.37)	10	9 (38.35)		6.3 %	6.00 [-29.42, 41.42]
Subtotal (95% CI)	**50**		**50**			**100.0 %**	**2.10 [-7.48, 11.68]**
Heterogeneity: Tau² = 51.97; Chi² = 7.77, df = 3 (P = 0.05); I² =61%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² =0.0%							

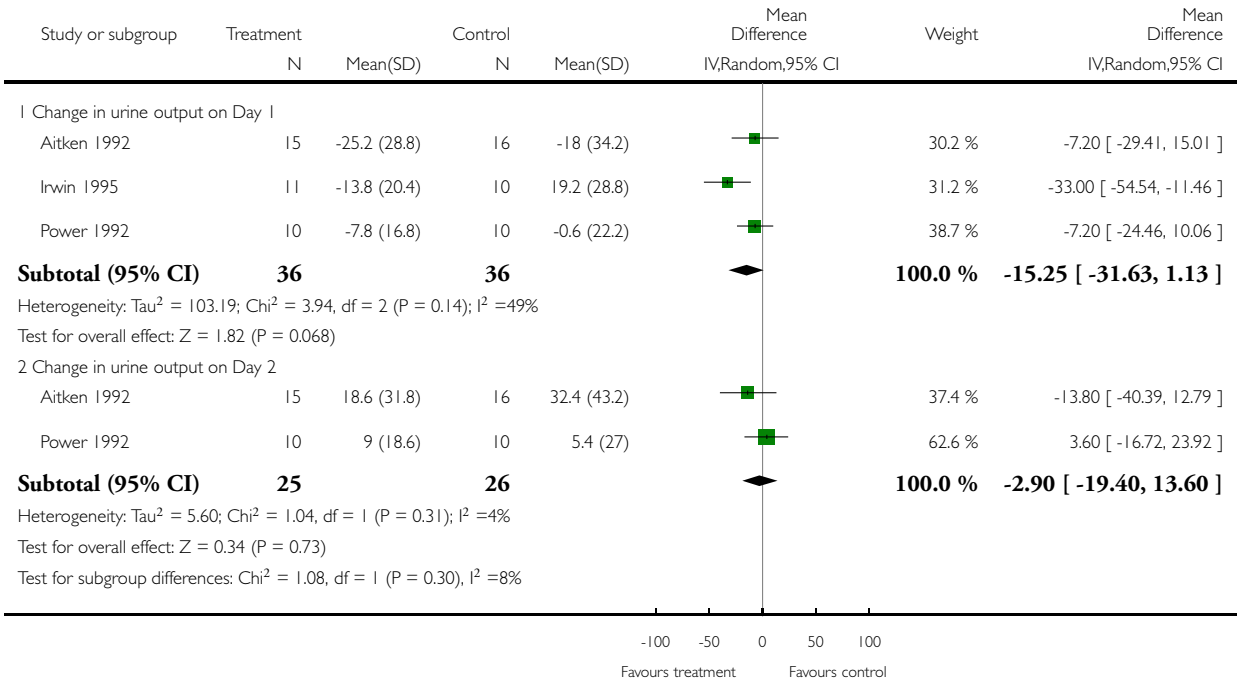


Analysis 1.3. Comparison 1 NSAIDs versus Placebo, Outcome 3 Change in urine volume (ml/h).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 3 Change in urine volume (ml/h)



Analysis 1.4. Comparison 1 NSAIDs versus Placebo, Outcome 4 Change in urinary sodium output (mmol/d).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 4 Change in urinary sodium output (mmol/d)

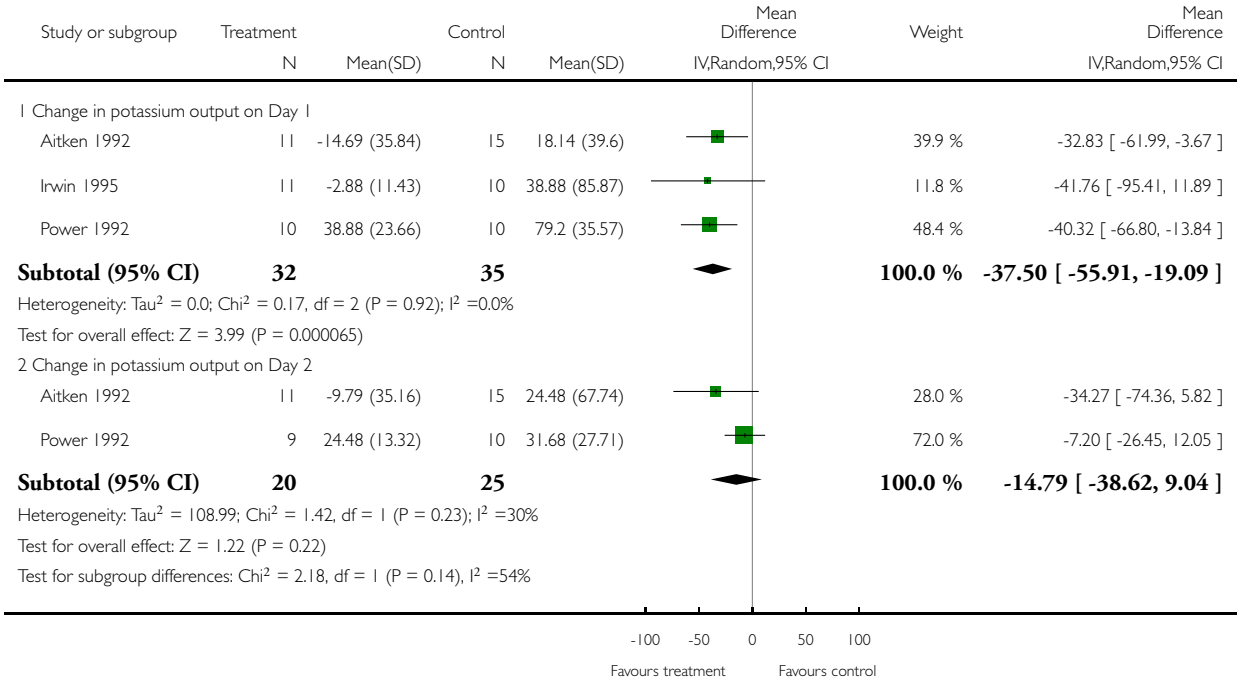
Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Change in sodium output on Day 1							
Aitken 1992	11	-95.62 (74.51)	15	-93.31 (87.29)		30.5 %	-2.31 [-64.68, 60.06]
Irwin 1995	11	-61.92 (46.81)	10	28.8 (113.88)		23.2 %	-90.72 [-166.53, -14.91]
Power 1992	10	-28.8 (55.96)	10	4.32 (41.74)		46.4 %	-33.12 [-76.39, 10.15]
Subtotal (95% CI)	**32**		**35**			**100.0 %**	**-37.07 [-79.43, 5.28]**
Heterogeneity: Tau^2 = 519.67; Chi^2 = 3.14, df = 2 (P = 0.21); I^2 =36%							
Test for overall effect: Z = 1.72 (P = 0.086)							
2 Change in sodium output on Day 2							
Aitken 1992	11	-76.75 (74.72)	15	-41.47 (90.24)		34.8 %	-35.28 [-98.80, 28.24]
Power 1992	9	-37.44 (55.66)	10	-38.88 (46.56)		65.2 %	1.44 [-44.98, 47.86]
Subtotal (95% CI)	**20**		**25**			**100.0 %**	**-11.34 [-48.82, 26.14]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%							
Test for overall effect: Z = 0.59 (P = 0.55)							
Test for subgroup differences: Chi^2 = 0.80, df = 1 (P = 0.37), I^2 =0.0%							

Analysis 1.5. Comparison 1 NSAIDs versus Placebo, Outcome 5 Change in urinary potassium output (mmol/d).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 5 Change in urinary potassium output (mmol/d)



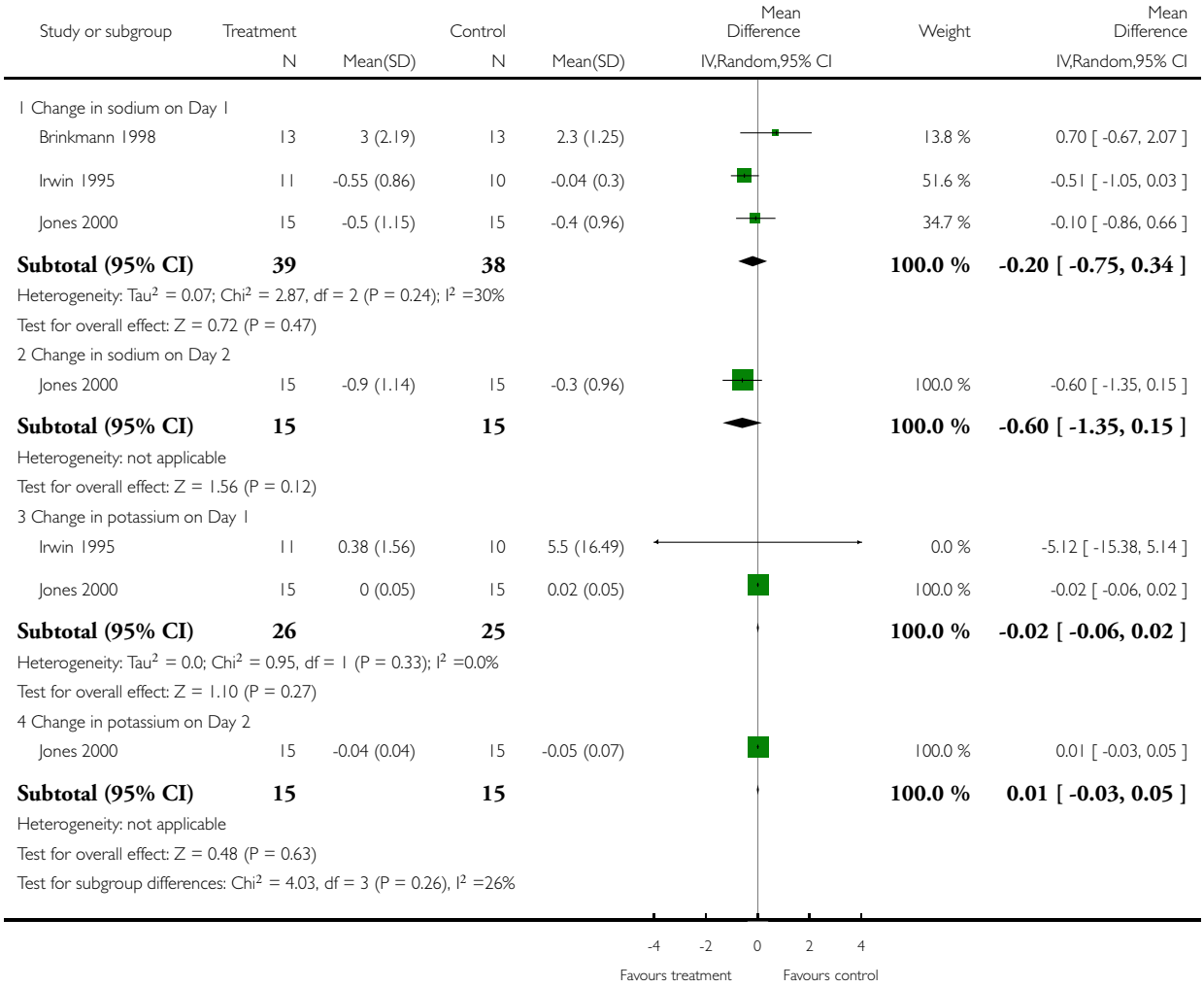
Analysis 1.6. Comparison 1 NSAIDs versus Placebo, Outcome 6 Change in fractional excretion of electrolyte (%).

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 6 Change in fractional excretion of electrolyte (%)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Change in sodium on Day 1							
Brinkmann 1998	13	3 (2.19)	13	2.3 (1.25)		13.8 %	0.70 [-0.67, 2.07]
Irwin 1995	11	-0.55 (0.86)	10	-0.04 (0.3)		51.6 %	-0.51 [-1.05, 0.03]
Jones 2000	15	-0.5 (1.15)	15	-0.4 (0.96)		34.7 %	-0.10 [-0.86, 0.66]
Subtotal (95% CI)	**39**		**38**			**100.0 %**	**-0.20 [-0.75, 0.34]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.87$, df = 2 (P = 0.24); $I^2 = 30\%$							
Test for overall effect: Z = 0.72 (P = 0.47)							
2 Change in sodium on Day 2							
Jones 2000	15	-0.9 (1.14)	15	-0.3 (0.96)		100.0 %	-0.60 [-1.35, 0.15]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.60 [-1.35, 0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.56 (P = 0.12)							
3 Change in potassium on Day 1							
Irwin 1995	11	0.38 (1.56)	10	5.5 (16.49)		0.0 %	-5.12 [-15.38, 5.14]
Jones 2000	15	0 (0.05)	15	0.02 (0.05)		100.0 %	-0.02 [-0.06, 0.02]
Subtotal (95% CI)	**26**		**25**			**100.0 %**	**-0.02 [-0.06, 0.02]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.95$, df = 1 (P = 0.33); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.10 (P = 0.27)							
4 Change in potassium on Day 2							
Jones 2000	15	-0.04 (0.04)	15	-0.05 (0.07)		100.0 %	0.01 [-0.03, 0.05]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**0.01 [-0.03, 0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Test for subgroup differences: $Chi^2 = 4.03$, df = 3 (P = 0.26), $I^2 = 26\%$							



Analysis 1.7. Comparison 1 NSAIDs versus Placebo, Outcome 7 Renal insufficiency requiring postoperative frusemide treatment.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 1 NSAIDs versus Placebo

Outcome: 7 Renal insufficiency requiring postoperative frusemide treatment

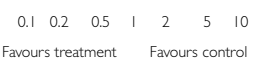
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brinkmann 1998	6/13	6/13		48.6 %	1.00 [0.44, 2.29]
Power 1992	9/10	4/10		51.4 %	2.25 [1.02, 4.94]
Total (95% CI)	**23**	**23**		**100.0 %**	**1.52 [0.68, 3.36]**

Total events: 15 (Treatment), 10 (Control)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 1.94$, df = 1 (P = 0.16); $I^2 = 48\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable



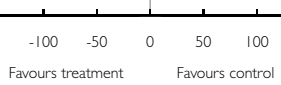
Analysis 2.1. Comparison 2 Multiple versus single NSAID dose regimen, Outcome 1 Change in creatinine clearance (ml/min) on Day 1.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 2 Multiple versus single NSAID dose regimen

Outcome: 1 Change in creatinine clearance (ml/min) on Day 1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Multiple NSAID doses versus placebo							
Aitken 1992	10	-24.1 (41.06)	15	-3.3 (40.71)		29.1 %	-20.80 [-53.54, 11.94]
Irwin 1995	11	-6 (27.87)	10	19 (34.77)		42.4 %	-25.00 [-52.12, 2.12]
Power 1992	10	1 (37.32)	10	29 (38.1)		28.5 %	-28.00 [-61.06, 5.06]
Subtotal (95% CI)	**31**		**35**			**100.0 %**	**-24.63 [-42.29, -6.98]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 2 (P = 0.95); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.73 (P = 0.0062)							
2 Single NSAID dose versus placebo							
Brinkmann 1998	13	3.6 (31.18)	13	17.8 (40.66)		30.0 %	-14.20 [-42.05, 13.65]
Jones 2000	15	18 (32.14)	15	21 (54.81)		22.5 %	-3.00 [-35.15, 29.15]
Slaven 1998	10	-20.8 (27.86)	9	-9.3 (21.19)		47.5 %	-11.50 [-33.63, 10.63]
Subtotal (95% CI)	**38**		**37**			**100.0 %**	**-10.40 [-25.65, 4.86]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.28$, df = 2 (P = 0.87); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.34 (P = 0.18)							
Test for subgroup differences: $Chi^2 = 1.43$, df = 1 (P = 0.23), $I^2 = 30\%$							



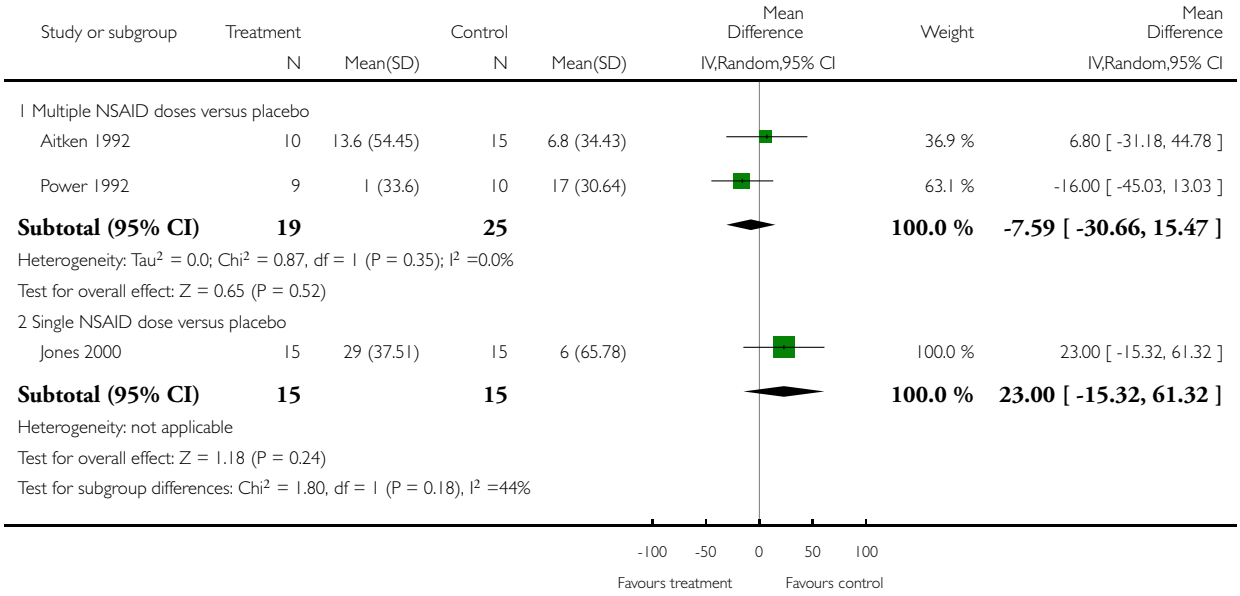
Analysis 2.2. Comparison 2 Multiple versus single NSAID dose regimen, Outcome 2 Change in creatinine clearance (ml/min) on Day 2.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 2 Multiple versus single NSAID dose regimen

Outcome: 2 Change in creatinine clearance (ml/min) on Day 2

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Multiple NSAID doses versus placebo							
Aitken 1992	10	13.6 (54.45)	15	6.8 (34.43)		36.9 %	6.80 [-31.18, 44.78]
Power 1992	9	1 (33.6)	10	17 (30.64)		63.1 %	-16.00 [-45.03, 13.03]
Subtotal (95% CI)	**19**		**25**			**100.0 %**	**-7.59 [-30.66, 15.47]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.65 (P = 0.52)							
2 Single NSAID dose versus placebo							
Jones 2000	15	29 (37.51)	15	6 (65.78)		100.0 %	23.00 [-15.32, 61.32]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**23.00 [-15.32, 61.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							
Test for subgroup differences: $Chi^2 = 1.80$, df = 1 (P = 0.18), $I^2 = 44\%$							

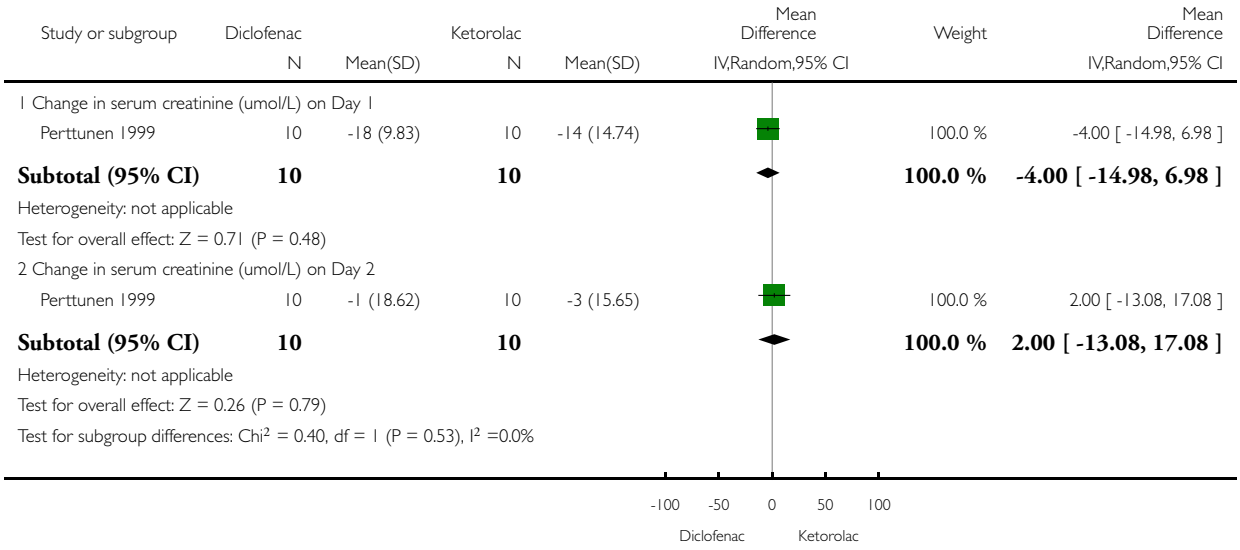


Analysis 3.1. Comparison 3 NSAID versus NSAID, Outcome 1 Diclofenac versus ketorolac.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 3 NSAID versus NSAID

Outcome: 1 Diclofenac versus ketorolac

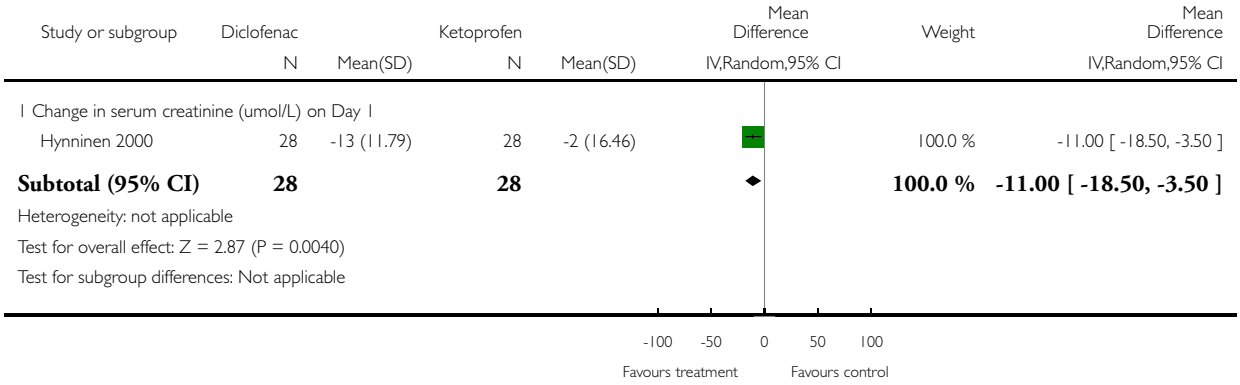


Analysis 3.2. Comparison 3 NSAID versus NSAID, Outcome 2 Diclofenac versus ketoprofen.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 3 NSAID versus NSAID

Outcome: 2 Diclofenac versus ketoprofen

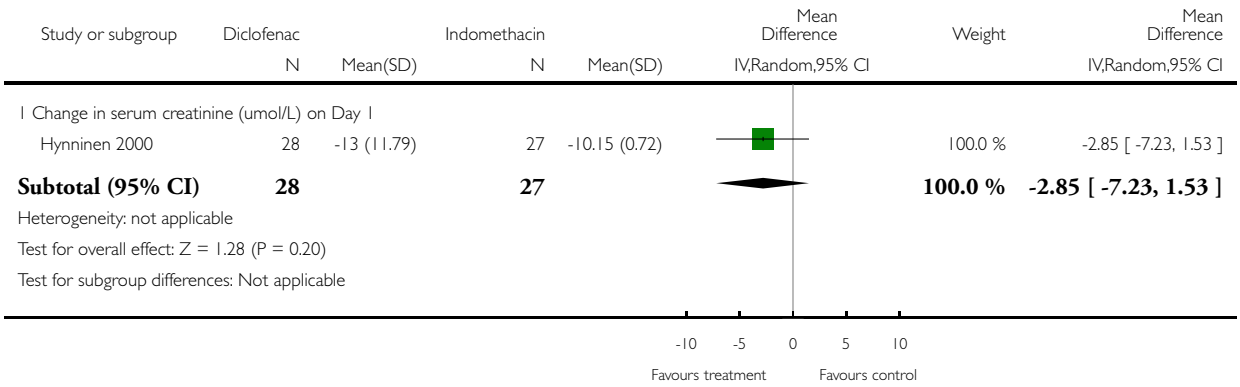


Analysis 3.3. Comparison 3 NSAID versus NSAID, Outcome 3 Diclofenac versus indomethacin.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 3 NSAID versus NSAID

Outcome: 3 Diclofenac versus indomethacin

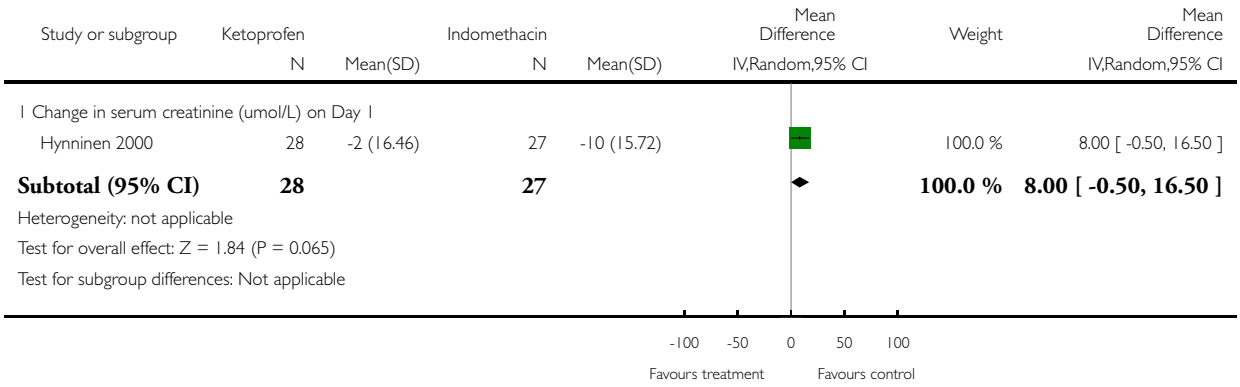


Analysis 3.4. Comparison 3 NSAID versus NSAID, Outcome 4 Ketoprofen versus indomethacin.

Review: Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function

Comparison: 3 NSAID versus NSAID

Outcome: 4 Ketoprofen versus indomethacin



WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 4, 2000

Date	Event	Description
19 January 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AL initiated and designed the study, extracted the data, conducted statistical analyses, wrote first draft of the review, collated comments from the other authors, and incorporated the comments of the Anaesthesia and Intensive Care and Cochrane peer reviewers into the final version. MCG provided input to the data extraction forms and extracted the data, and commented on all drafts of the review. JCC, JPK and JFK provided input to the design of the study and commented on all drafts of the review.

DECLARATIONS OF INTEREST

There was no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong.

External sources

- No sources of support supplied

NOTES

This work was done at the Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*adverse effects]; Creatinine [blood]; Kidney [*drug effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Renal Insufficiency [etiology]

MeSH check words

Adult; Humans